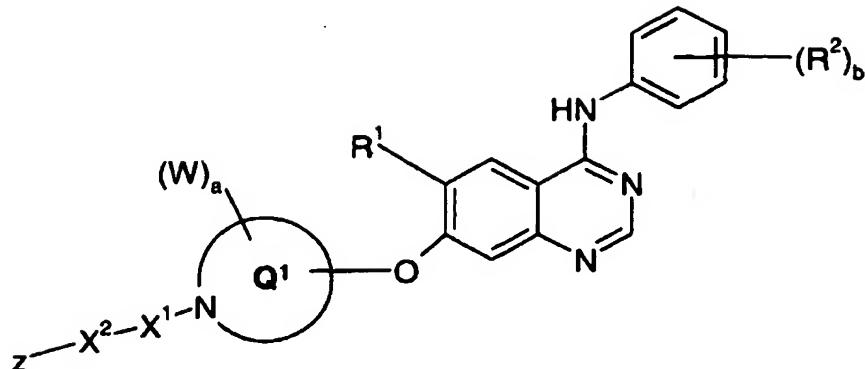


CLAIMS**1. A quinazoline derivative of the Formula I:**

5 wherein:

R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyoxy, or from a group of the formula :

Q²-X³-

wherein X³ is a direct bond or is O, and Q² is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl,

10 (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or

heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R³), CO, CH(OR³), CON(R³), N(R³)CO, SO₂N(R³), N(R³)SO₂, CH=CH and
15 C≡C wherein R³ is hydrogen or (1-6C)alkyl,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or

20 from a group of the formula :

Q³-X⁴-

wherein X⁴ is a direct bond or is selected from CO and N(R⁴)CO, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q³ is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent, other than a CH₂ group

25 within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more

halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino,

carboxy, carbamoyl, sulfamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio,
 (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
 (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,
 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

5 N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl,
N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:
 $-X^5-Q^4$

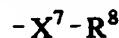
wherein X^5 is a direct bond or is selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵),
10 CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, C(R⁵)₂O, C(R⁵)₂S and C(R⁵)₂N(R⁵), wherein R⁵ is
hydrogen or (1-6C)alkyl, and Q⁴ is (3-7C)cycloalkyl, (3-7C)cycloalkyl-
(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or
heterocyclyl-(1-6C)alkyl,
and wherein any heterocyclyl group within a substituent on R¹ optionally bears one or
15 more substituents, which may be the same or different, selected from halogeno,
trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto,
sulfamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy,
(2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl,
(1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
20 N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl,
N,N-di-[(1-6C)alkyl]sulfamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl,
N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and
N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:
 $-X^6-R^6$

wherein X⁶ is a direct bond or is selected from O, N(R⁷) and C(O), wherein R⁷ is hydrogen or
(1-6C)alkyl, and R⁶ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl,
(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,
(1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,
30 (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl,
N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or
(1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocycl group within a substituent on R¹ optionally bears 1 or 2 oxo or thioxo substituents;

b is 1, 2, 3, 4 or 5;

each R², which may be the same or different, is selected from halogeno, cyano, nitro, 5 hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, 10 N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula :

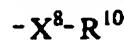


wherein X⁷ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, 15 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl;

Q¹ is piperidinyl;

a is 0, 1, 2, 3 or 4;

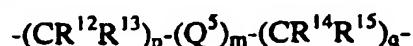
20 each W, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, oxo, amino, formyl, mercapto, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:



25 wherein X⁸ is a direct bond or is selected from O, CO, SO₂ and N(R¹¹), wherein R¹¹ is hydrogen or (1-6C)alkyl, and R¹⁰ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N-(1-6C)alkylamino-(1-6C)alkyl or N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl;

X¹ is selected from CO and SO₂;

30 X² is a group of the formula:



wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R¹², R¹³, R¹⁴ and R¹⁵, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q⁵ is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said 5 CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino,

N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:

10 Q⁶-X⁹-

wherein X⁹ is a direct bond or is selected from O, N(R¹⁶), SO₂ and SO₂N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and Q⁶ is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl;

15 provided that when X⁹ is a direct bond, Q⁶ is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹⁷), CO, -C=C- and -C≡C- wherein R¹⁷ is hydrogen or (1-6C)alkyl,

20 and wherein and wherein any CH₂ or CH₃ group within any Z group, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino,

25 di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

(2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl,

N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and

N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

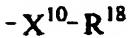
30 and wherein any heterocyclyl group within a Z substituent optionally bears one or

more substituents which may be the same or different, selected from halogeno,

trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl,

(2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl,

(1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:



wherein X^{10} is a direct bond or is selected from O, CO, SO₂ and N(R¹⁹), wherein R¹⁹ is 5 hydrogen or (1-4C)alkyl, and R¹⁸ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl; provided that:

when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-10 fluoroanilino and R¹ is hydrogen or (1-3C)alkoxy, then a is 0 and Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q⁶-X⁹-;

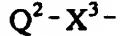
or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

15

2. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein:

R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

20



wherein X³ is a direct bond or is O, and Q² is heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R³), CON(R³), N(R³)CO, CH=CH and C≡C wherein R³ is hydrogen or (1-6C)alkyl, and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl and wherein any CH₂ or CH₃ group within a R¹ substituent, other than a CH₂ group

30 within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano, carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :

-135-

$-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O, N(R^5), CON(R^5), N(R^5)CO and C(R^5)₂O, wherein R^5 is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or

5 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, or from a group of the formula:

$-X^6-R^6$

10 wherein X^6 is a direct bond or is selected from O and N(R^7), wherein R^7 is hydrogen or (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,
and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2

15 oxo substituents.

3. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein:

R^1 is selected from hydrogen, hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-

20 3C)alkoxy-(2-4C)alkoxy or from a group of the formula :

Q^2-X^3-

wherein X^3 is O, and Q^2 is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or

25 3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, and (2-4C)alkanoyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 oxo substituent.

30

4. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein R^1 is (1-3C)alkoxy.

5. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein:

b is 1, 2 or 3; and

5 each R², which may be the same or different, is selected from fluoro, chloro, bromo, (1-4C)alkyl, (2-4C)alkenyl and (2-4C)alkynyl.

6. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims

10 wherein:

b is 1, 2 or 3 and one R² is at the meta (3-) position on the anilino group in Formula I and is halogeno.

7. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a

15 pharmaceutically acceptable ester thereof, according to any one of claims 1 to 4 wherein the anilino group at the 4-position on the quinazoline ring in the compound of Formula I is selected from 3-chloro-2-bromoanilino, 3-chloro-2-fluoroanilino, 3-ethynylanilino and 3-bromoanilino.

20 8. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein:

X² is a group of the formula -(CR¹²R¹³)_q-(CR^{12aa}R^{13aa})-, wherein

q is 1, 2 or 3,

25 each of R¹², R¹³ and R^{13aa}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

R^{12aa} is selected from amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno substituents,

30 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

9. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of claims 1 to 7 wherein:

X² is a group of the formula -(CR¹²R¹³)_q-, wherein

5 q is 1, 2, 3 or 4,

each of R¹² and R¹³, which may be the same or different, is selected from hydrogen and (1-6C)alkyl, provided that at least one of the R¹² or R¹³ groups in X² is (1-6C)alkyl, and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno substituents,

10 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, and (1-6C)alkoxy.

15 10. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of claims 1 to 7 wherein:

X² is selected from a group of the formula -CH₂-,-CH₂CH₂-,-(CHR^{12a})-,-(CHR^{12a}CH₂)-,-(C(R^{12a})₂CH₂)-,-(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12a})-, wherein each R^{12a}, which may be the same or different, is (1-4C)alkyl.

20 11. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein:

Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy and a group of the formula:

25 Q⁶-X⁹-

wherein X⁹ is a direct bond and Q⁶ is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl linked to X¹ by a ring carbon atom,

and wherein any heterocyclyl group in Z is selected from azetidinyl, tetrahydrofuran-1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl,

and wherein and wherein any CH₂ or CH₃ group within a Z group, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or

more halogeno or (1-4C)alkyl substituents or a substituent selected from hydroxy and (1-4C)alkoxy,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more substituents which may be the same or different, selected from halogeno,

5 trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino and (2-4C)alkanoyl.

12. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims

10 wherein:

Z is hydroxy or (1-4C)alkoxy; and

the sum of m +p+q is at least 1.

13. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a

15 pharmaceutically acceptable ester thereof, according to any one of claims 1 to 7 wherein:

X² is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR^{12a})-, -(CH₂CHR^{12a}CH₂)-, -(C(R^{12a})₂CH₂)-, -(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12a})-,
wherein each R^{12a}, which may be the same or different, is (1-4C)alkyl; and
Z is hydroxy or (1-4C)alkoxy.

20

14. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims
wherein:

Q¹ is piperidin-4-yl;

25 a is 0 or 1; and

W is selected from halogeno, hydroxy, (1-3C)alkyl and (1-3C)alkoxy.

15. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims

30 wherein X¹ is CO.

16. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein:

BEST AVAILABLE COPY This Page Blank (uspto)

R¹ is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,
and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
5 said CH₂ or CH₃ group one or more halogeno substituents, or a substituent selected from hydroxy and (1-4C)alkoxy;

b is 1, 2 or 3;
each **R²**, which may be the same or different, is selected from halogeno, cyano, hydroxy, trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl and (1-4C)alkoxy;

10 **Q¹** is piperidin-4-yl;
a is 0, 1 or 2;
each **W**, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, oxo, (1-6C)alkyl, (1-6C)alkoxy, and from a group of the formula:

$$-X^8-R^{10}$$

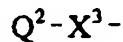
15 wherein **X⁸** is a direct bond or is O, and **R¹⁰** is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;
X¹ is CO;
X² is a group selected from (3-6C)cycloalkylene, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -(CR¹²R¹³)-, -(CR¹²R¹³CH₂)- and -(CH₂CR¹²R¹³)-,

20 wherein each of **R¹²** and **R¹³**, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl, provided that **R¹²** and **R¹³** are not both hydrogen,
and wherein any CH₂ group within a (3-6C)cycloalkylene group in **X²**, optionally bears on each said CH₂ or group one or more (1-4C)alkyl substituents or a substituent selected
25 from hydroxy, (1-4C)alkoxy, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl; and
Z is selected from hydroxy and (1-4C)alkoxy;
provided that:
when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino, **R¹** is hydrogen or (1-3C)alkoxy, and **X¹** is CO, then **a** is 0.

30 17. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein:

the 4-anilino group on the quinazoline ring in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino, 3-bromoanilino and 3-ethynylanilino;

R^1 is selected from (1-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-3C)alkoxy-(2-4C)alkoxy
5 or from a group of the formula:



wherein X^3 is O, and Q^2 is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or
10 3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino,
(1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

Z is hydroxy or (1-4C)alkoxy;

Q^1 is piperidin-4-yl;

a is 0 or 1;

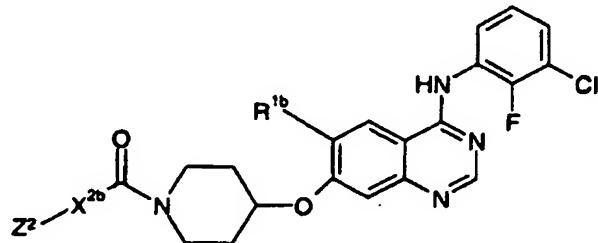
15 each W , which may be the same or different is selected from hydroxy, (1-3C)alkyl and (1-3C)alkoxy;

X^1 is CO;

X^2 is selected from a group of the formula $-(CHR^{12a})-$ and $-(CH_2CHR^{12b})-$,
wherein R^{12a} is (1-4C)alkyl,

20 and wherein R^{12b} is selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-
amino.

18. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 of the Formula Id:



25

wherein:

R^{1b} is (1-4C)alkoxy,

BEST AVAILABLE COPY - WWW.VISUALS.UK/

and wherein any CH_2 or CH_3 group within a R^{1b} substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents, or any CH_2 or CH_3 group within a R^1 which is not attached to an oxygen atom optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy and (1-3C)alkoxy;

5 X^{2b} is selected from a group of the formula $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-(\text{CHR}^{12})-$, $-(\text{CHR}^{12}\text{CH}_2)-$ and $-(\text{CH}_2\text{CHR}^{12})-$

wherein R^{12} is selected from (1-3C)alkyl, hydroxy-(1-3C)alkyl and (1-3C)alkoxy-(1-3C)alkyl; and

10 Z^2 is selected from hydroxy, (1-3C)alkoxy, hydroxy-(2-3C)alkoxy, (1-3C)alkoxy-(2-3C)alkoxy, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl and 1,4-dioxanyl;

and wherein any heterocyclyl group within $\text{Z}^2\text{-X}^{2b}$ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-3C)alkyl, (1-3C)alkoxy and (2-3C)alkanoyl;

15 or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

19. A quinazoline derivative according to claim 18, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, wherein Z^2 is hydroxy and R^{12} is (1-3C)alkyl;

20 20. A quinazoline derivative according to claim 18, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, wherein:

R^{1b} is (1-3C)alkoxy; and

the group $\text{Z}^2\text{-X}^{2b}$ is selected from hydroxymethyl, methoxymethyl, (S)-1-hydroxyethyl, (R)-1-hydroxyethyl, (S)-1-methoxyethyl and (R)-1-methoxyethyl.

25

21. A quinazoline derivative of the Formula I according to claim 1 selected from:

N -(3-chloro-2-fluorophenyl)-7-({1-[[(dimethylamino)acetyl]piperidin-4-yl}oxy)-6-methoxyquinazolin-4-amine;

N -(3-chloro-2-fluorophenyl)-6-methoxy-7-({1-[(2-methoxyethoxy)acetyl]piperidin-4-

30 yl}oxy)quinazolin-4-amine;

N -(3-chloro-2-fluorophenyl)-6-methoxy-7-{{1-(methoxyacetyl)piperidin-4-yl}oxy}quinazolin-4-amine;

2-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-2-oxoethanol;

N-(3-chloro-2-fluorophenyl)-7-[(1-ethoxycetyl)piperidin-4-yl]oxy]-6-methoxyquinazolin-4-amine;

5 N-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(1-(3-methoxyprop酰))piperidin-4-yl]oxy}quinazolin-4-amine;

3-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-3-oxopropan-1-ol;

(2S)-1-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-1-10 oxopropan-2-ol;

(2S,3S)-1-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-3-methyl-1-oxopentan-2-ol;

4-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-2-methyl-4-oxobutan-2-ol;

15 N-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl)oxy}quinazolin-4-amine;

3-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-2,2-dimethyl-3-oxopropan-1-ol;

(3R,5S)-1-acetyl-5-[(4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]carbonyl]pyrrolidin-3-ol; and

20 N-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(1-[(4-methylpiperazin-1-yl)acetyl]piperidin-4-yl)oxy}quinazolin-4-amine;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

25 22. A quinazoline derivative of the Formula I selected from:

N-(3-Chloro-2-fluorophenyl)-6-methoxy-7-[(1-(methoxycetyl)piperidin-4-yl)oxy}quinazolin-4-amine;

2-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-2-oxoethanol;

30 N-(3-chloro-2-fluorophenyl)-7-[(1-ethoxycetyl)piperidin-4-yl]oxy}-6-methoxyquinazolin-4-amine;

(2S)-1-[4-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl)oxy)piperidin-1-yl]-1-oxopropan-2-ol;

3-[4-(*{4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-2,2-dimethyl-3-oxopropan-1-ol;

(2*S*)-1-[4-(*{4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-3,3-dimethyl-1-oxobutan-2-ol;

5 *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-*{[1-(1-methyl-L-prolyl)piperidin-4-yl]oxy}*quinazolin-4-amine;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-*{[1-[(2*S*)-tetrahydrofuran-2-ylcarbonyl]piperidin-4-yl]oxy}*quinazolin-4-amine;

(2*R*)-1-[4-(*{4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-1-

10 oxopropan-2-ol;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-*{[1-[(2*S*)-2-methoxypipropanoyl]piperidin-4-yl]oxy}*quinazolin-4-amine;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-*{[1-[(2*R*)-2-methoxypipropanoyl]piperidin-4-yl]oxy}*quinazolin-4-amine;

15 (2*R*)-3-[4-(*{4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-2-(dimethylamino)-3-oxopropan-1-ol;

(2*S*)-1-[4-(*{4-[3-chloro-4-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-1-

oxopropan-2-ol;

(2*S*)-1-[4-(*{4-[3-bromoanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-1-oxopropan-

20 2-ol;

(2*S*)-1-[4-(*{4-[3-bromo-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-1-

oxopropan-2-ol;

(2*R*)-1-[4-(*{4-[3-bromo-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-1-

oxopropan-2-ol; and

25 (2*R*)-1-[4-(*{4-[3-bromoanilino]-6-methoxyquinazolin-7-yl}oxy*)piperidin-1-yl]-1-oxopropan-2-ol;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

23. A quinazoline derivative of the Formula I according to any one of the preceding

30 claims, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester

thereof, according to any one of the preceding claims, in association with a pharmaceutically acceptable diluent or carrier.

25. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a
5 pharmaceutically acceptable ester thereof, according to any one of claims 1 to 23, for use as a
medicament.

26. Use of a quinazoline derivative of the Formula I, a pharmaceutically acceptable salt, or a
pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23 in the
10 manufacture of a medicament for use in the production of an anti-proliferative effect in a
warm-blooded animal such as a human.

27. Use of a quinazoline derivative of the Formula I, a pharmaceutically acceptable salt, or a
pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23 in the
15 manufacture of a medicament for use in the prevention or treatment of those tumours which
are sensitive to inhibition of EGFR tyrosine kinases, that are involved in the signal
transduction steps which lead to the proliferation of tumour cells.

28. Use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt,
20 or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23 in the
manufacture of a medicament for use in providing a selective EGFR tyrosine kinase inhibitory
effect in a warm-blooded animal such as a human.

29. Use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt,
25 or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23 in the
manufacture of a medicament for use in the treatment of a cancer in a warm-blooded animal
such as a human.

30. A method for producing an anti-proliferative effect in a warm-blooded animal, such as
30 a human, in need of such treatment which comprises administering to said animal an effective
amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or
a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23.

BEST AVAILABLE COPY

31. A method for the prevention or treatment of those tumours in a warm-blooded animal such as a human which are sensitive to inhibition of EGFR tyrosine kinases, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23.

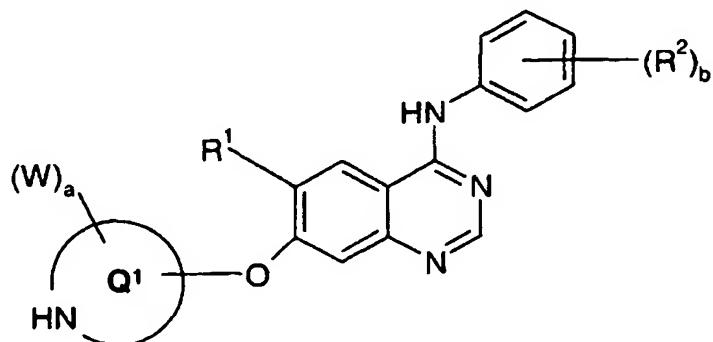
32. A method for providing a selective EGFR tyrosine kinase inhibitory effect in a warm-blooded animal such as a human which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23.

33. A method for treating a cancer in a warm-blooded animal, such as a human, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 23.

34. A process for the preparation of a quinazoline derivative of the Formula I as defined in Claim 1 which comprises:

20 Process (a):

for the preparation of compounds of the Formula I wherein X^1 is CO, the coupling of a quinazoline of the formula II or a salt thereof:



II

25 wherein R^1 , R^2 , W , a , b and Q^1 are as defined in claim 1, except that any functional group is protected if necessary, with an acid of the formula III, or a reactive derivative

thereof:



III

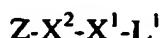
wherein Z and X² are as defined in claim 1, except that any functional group is

5 protected if necessary;

or

Process (b) the reaction of a quinazoline of the formula **II** or a salt thereof, as defined in relation to Process (a), with a compound of the formula **IV**:

10

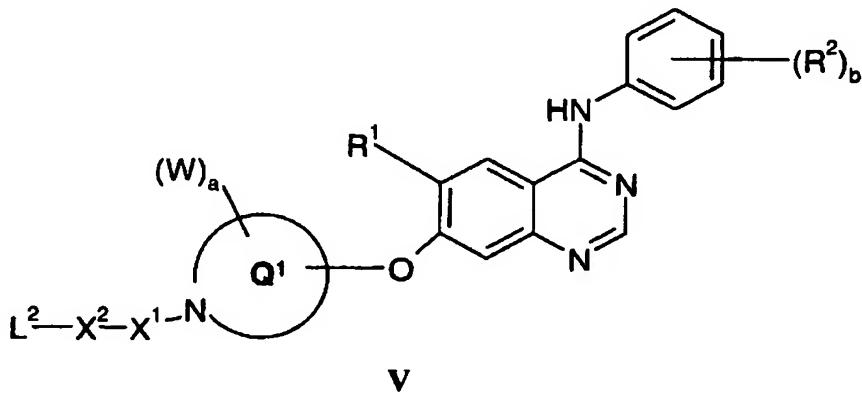


IV

wherein L' is a displaceable group and Z, X¹ and X² are as defined in claim 1, except that any functional group is protected if necessary;

or

15 Process (c) for the preparation of those quinazoline derivatives of the Formula I wherein Z is linked to X² by nitrogen, the reaction of a compound of the formula **V**:



wherein L² is a displaceable group and R¹, R², W, X¹, X², a, b and Q¹ are as defined in claim 1, except that any functional group is protected if necessary, with a compound of the

20 formula ZH, wherein Z is as hereinbefore defined, except that any functional group is protected if necessary; or

Process (d)

for the preparation of those quinazoline derivatives which carry a mono- or di-(1-6C)alkylamino group, the reductive amination of the corresponding quinazoline derivative of
25 the Formula I which contains an N-H group using formaldehyde or a (2-6C)alkanolaldehyde; or

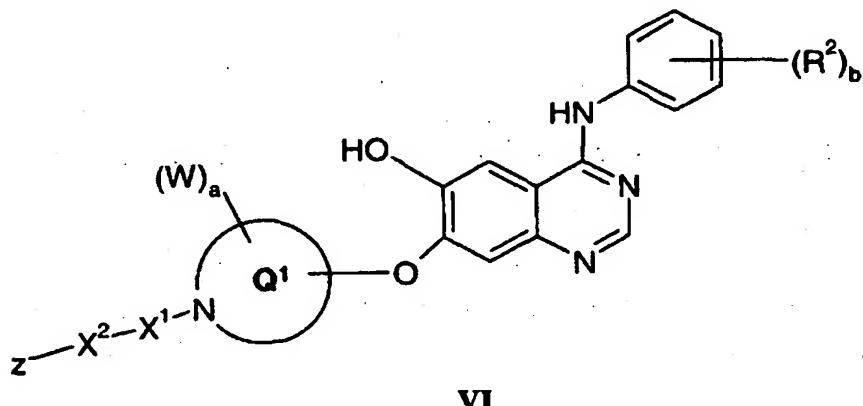
DEJ1 AVAILABLE COPY

Process (e)

for the preparation of those quinazoline derivatives of the Formula I wherein R¹ is hydroxy, the cleavage of a quinazoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy group; or

5 Process (f)

for the preparation of those quinazoline derivatives of the Formula I wherein R¹ is linked to the quinazoline ring by an oxygen atom, by coupling a compound of the Formula VI:



10 wherein R², W, X¹, X², Z, a, b and are as defined in claim 1 except that any functional group is protected if necessary, with a compound of the formula R^{1'}OH, wherein the group R^{1'}O is one of the oxygen linked groups as defined for R¹ in claim 1, except that any functional group is protected if necessary;

and thereafter, if necessary (in any order):

15 (i) converting a quinazoline derivative of the Formula I into another quinazoline derivative of the Formula I;
(ii) removing any protecting group that is present by conventional means; and
(iii) forming a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester of the quinazoline derivative of the Formula I.

20

35. A quinazoline derivative of the Formula II: